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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,198	10/17/2003	Gerardo Zapata	ABGENIX.057A	6664

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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
06/19/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/688,198	ZAPATA, GERARDO	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-11,13-23 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-11, 13-23 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-3, 5-11, 13-23 and 25 are all the pending claims for this application.

2. Claim 19 is amended in the Response of 3/24/08.

3. Claims 1-3, 5-11, 13-23 and 25 are all the pending claims under examination.

4. Applicants allegations of record have raised new grounds for consideration and rejection.

Withdrawal of Rejections

Claim Rejections - 35 USC § 102

5. The rejection of Claims 1-7, 10, 13 and 16 under 35 U.S.C. 102(b) as being anticipated by van Erp et al. (J. Biotechnol. 20:249-262 (1991)) as evidenced by Sigma data sheet for pepstatin A (3/19/01) is withdrawn.

Applicants' allegations on pp. 5-6 of the Response of 3/24/08 have been carefully considered and are found persuasive. Applicants allege "van Erp fails to teach adjustments of a cell line to activate endogenous proteases to produce antigen-binding fragments. van Erp's disclosure is limited to pH adjustment of supernatant, and not cell media as recited in the claims, and van Erp does not teach or suggest "incubating said cell line under the adjusted pH conditions. Van Erp only teaches adjusting the supernatant that does not contain any cells."

Claim Rejections - 35 USC § 103

6. The rejection of Claims 1, 8, 9, 11, 17, 18, 19, 21-23 and 25 under 35 U.S.C. 103(a) as being unpatentable over van Erp et al. (J. Biotechnol. 20:249-262 (1991)) in view of Kratje et al. (J. Biotechnol. 32:107-125 (1994)) and Mason et al. (Protein Expression and Purification 23:45-54 (2001); cited in the PTO 892 form of 6/22/06) as evidenced by Sigma data sheet for pepstatin A (3/19/01) is withdrawn.

Applicants' allegations on pp. 5-6 of the Response of 3/24/08 have been carefully considered and are found persuasive. Applicants allege "van Erp fails to teach pH adjustments of a cell line to activate endogenous proteases to produce antigen-binding antibody fragments." "Kratje discloses the proteolytic capacities of the proteases secreted in culture supernatants but fails to teach or disclose the generation of antigen-binding fragments of an antibody from an antibody-producing cell-line growing in a cell media under conditions to express antibodies by adjusting the pH conditions of the cell media." "Mason fails to fill the void in the disclosure left by van Erp and Kratje."

7. The rejection of Claims 1, 14, 15, 19 and 20 under 35 U.S.C. 103(a) as being unpatentable over van Erp et al. (J. Biotechnol. 20:249-262 (1991)) in view of Kratje et al. (J. Biotechnol. 32:107-125 (1994)) as applied to claims 1 and 19 above, and further in view of Zhang et al (Cytotechnology 16:147-150 (1994); cited in the PTO 892 form of 6/22/06) and Schifferli et al. (Focus 21:16-17 (1999); cited in the PTO 892 form of 6/22/06) is withdrawn.

Applicants' allegations on pp. 5-6 of the Response of 3/24/08 have been carefully considered and are found persuasive. Applicants allege "neither Zhang or Schifferli complete the gaps in disclosure left by van Erp and Kratje."

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

8. Claims 1-3, 5-11, 13-23 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for generating antibody fragments in conditioned, cell cultured media or supernatant from antibody-producing cells by adjusting pH and temperature of the media, does not reasonably provide enablement for culturing antibody-producing cells in a culture medium adjusted to about pH 3.5 and/or changed to any temperature in order to produce antibody fragments without affecting cell viability or the ability of the cells to produce antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They

include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention/ Skill in the Art

Claims 1-3, 5-11 and 13-18 are interpreted as being broadly drawn to a method for generating antibody-binding fragments where an antibody-producing cell line is growing in cell media under conditions to express antibodies, and the cell media is pH-adjusted to activate at least one endogenous enzyme in the medium that cleaves the antibodies, and the cell line is incubated under the pH-adjusted conditions so that the antibodies are cleaved into antigen-binding fragments.

Claims 19-23 and 25 are interpreted as being broadly drawn to a method for producing F(ab')2 fragments of an antibody where an antibody producing cell line is grown in a cell media to produce the antibody and endogenous cysteinyl enzyme activity in the cell media is inactivated and endogenous aspartyl enzyme activity in the cell media is activated by adjusting pH conditions of the cell media comprising the cell line in order to cleave the produced antibody into F(ab')2 fragments.

The relative skill in the art required to practice the invention is a bio-manufacturer with a background in cell culture fermentation and antibody isolation techniques.

Disclosure in the Specification

The specification does not disclose culturing any kind of antibody-producing cell in a cell culture medium and adjusting the pH and/or temperature in the presence of the whole living cells in order to generate antigen-binding fragments. Applicants are required to identify by citation of the exact page, paragraph and line number for an example that supports the instant claimed method. Otherwise, the specification teaches "The cell culture may be harvested by removing particulate matter and cells using depth filtration. After clarification, the cell culture media may be concentrated approximately 10X and stored prior to digestion [0042]; clarification of the cell culture media [0043, 0049, 0052, 0058, 0059, 0066] and harvesting cell culture supernatant by filtration and centrifugation prior to being subjected to the pH treatments [0047, 0048]. Thus the ordinary artisan could not practice the method with the presence of whole cells without effecting the antibody production by the cells where the cells were required to produce antibodies in the cell medium under culture conditions adjusted to a low pH and a high temperature. The specification does not demonstrate that generating antigen-binding F(ab')2 fragments could be produced by another means than from a clarified, conditioned supernatant that was pH- and temperature-adjusted.

Prior Art Status: Cell Culture Conditions for Antibody-producing Cells is Optimized

The antibody-producing cells of the method invention include CHO, HeLa, baby hamster kidney cells, monkey kidney cells and human hepatocellular carcinoma cells. It is unpredictable that any of these cell lines could produce antibody in a cell media adjusted to a pH of about 3.5 and/or adjusted to any temperature without compromising

the ability of the cell line to produce antibody much less the viability of the cell. The data sheets for the exemplary cell lines were obtained from the ATCC website where for each cell line, the propagation conditions are described (see attached product datasheets). None of the propagation conditions teach or suggest any cell line having a growth tolerance outside of a physiological pH and a physiological temperature range. Thus absent a further showing of unexpected properties for any of these cell lines in the hands of the inventors, the ordinary artisan could not practice the method invention where the antibody-producing cells were still present in the culture after the cell media had been adjusted to a pH of about pH 3.5 and the temperature had been generally adjusted more or less. Applicants' specification is insufficient in its guidance and in view of the absence of any working examples using the exemplary cell lines under the culture conditions as instantly claimed, it is unpredictable that the ordinary artisan could practice the methods without having to perform additional experimentation in order to optimize the cultured cells to perform under the claimed requirements.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Examiner, Art Unit 1643
Temporary Partial Signatory Authority